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Radiologic and Audiologic Findings in the Temporal Bone of Patients with CHARGE Syndrome

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Background: CHARGE syndrome is a common congenital anomaly. Hearing loss affects 60%-90% of these children. As temporal bone computed tomography (CT) has become more sophisticated, more abnormalities of the middle and inner ear have been found. We present the detailed CT findings for children with CHARGE syndrome and the correlation of the CT findings with audiograms.

Methods: We performed a retrospective medical records review of 12 patients with CHARGE syndrome, identified between 1990-2011 at Princess Margaret Hospital for Children in Western Australia, who underwent temporal bone CT for evaluation of hearing loss.

Results: We present our findings for the 24 ears in terms of the cochlear, semicircular canal, middle ear, facial nerve, external auditory canal, venous, and jugular anomalies. The internal auditory canal was normal in 83.3% (n=20) of ears. Three (12.5%) ears had enlarged basal turns, and 4 (16.7%) each had hypoplastic and incompletely partitioned apical turns. The majority (n=13, 56.5%) of the vestibules were dysplastic. Up to 70.8% had abnormalities of the semicircular canal. The middle ear cavity was normal in 55% (n=11) of ears; however, up to 80% of the ears had some abnormality of the ossicles, and up to 70% had an abnormality of the facial nerve (7th cranial nerve) segments, especially in the labyrinthine segment. CT findings did not correlate with the audiograms.

Conclusion: The management of children with CHARGE syndrome is complex, requiring early evaluation and close attention of the multidisciplinary team. Early identification of hearing deficits is vital for patients' linguistic development.

Keywords: *CHARGE syndrome, ear diseases, ear–inner, ear–middle, radiology, tomography–x-ray computed*

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INTRODUCTION

Hubert von Lushka noted the constellation of cardiac, central nervous system, and genitourinary defects and choanal atresia in an infant who died soon after birth in 1859.[1] The association was then defined by Hall and by Hittner et al independently in 1979.[2,3] In 1981, after reviewing the cases of 21 children, Pagon et al first proposed the diagnostic criteria for CHARGE syndrome to describe the nonrandom association of ocular coloboma (C), congenital heart defects (H), choanal atresia or stenosis (A), central nervous system/developmental anomalies (R), genital hypoplasia (G), and ear anomalies (E).[4] Since then, several cases and updates have been published.[5-25] Facial nerve and renal anomalies are considered common adjuncts to this spectrum.[1,26]

The diagnostic criteria have evolved over time, with the most recent revision by Sanlaville and Verloes.[5] The diagnosis requires the child to have 3 major criteria or 2 major and 2 minor criteria. The major criteria include ocular coloboma, choanal atresia, and semicircular canal hypoplasias. The minor criteria include rhombencephalic dysfunction, hypothalamo-hypophyseal dysfunction, ear malformation, mediastinal organ malformation, and mental retardation.[5]

CHARGE syndrome is a common congenital anomaly with an estimated incidence of 1:12,000, and a prevalence of 1:10,000.[5,7,14,16,18,27] While most cases are sporadic, there are reports of isolated chromosomal anomalies, autosomal dominant disorder in rare familial cases, and a high concordance rate in monozygotic twins.[5,6,12,14,18,22-24,28] Mutations of the CHD7 gene on chromosome 8q12 have been identified in 60%-70% of cases.[5,17,18,25,27] These chromodomain helicase DNA (CHD) binding proteins affect a large number of developmental pathways, resulting in the varied phenotypic spectrum observed in CHARGE syndrome.[5,18,25,26]

Hearing loss affects 60%-90% of children with CHARGE syndrome, with presentations of severe conductive or mixed hearing loss. Audiograms are uniquely wedge shaped with a low-frequency conductive hearing loss because of ossicular anomalies and a high-frequency sensorineural hearing loss.[5,8,11,13,16,17,19,21,23-25,29] Davenport et al published the first review of external ear malformations and suggested the existence of anomalies in every segment of the auditory system.[30] As temporal bone computed tomography (CT) has become more sophisticated, more abnormalities of the middle and inner ear have been found to contribute to the mixed hearing loss seen in these children, and these abnormalities have been described by several authors.[6,8-11,13,17,19-22,24-26,28-29,31,32] Inner ear anomalies are reported in 90% of children with CHARGE syndrome, with the absence or hypoplasia of one or all of the semicircular canals and a hypoplastic incus proposed to be the most specific anomalies for CHARGE syndrome.[10,25]

Quantifying hearing in a timely manner is important for children with CHARGE syndrome to facilitate early hearing rehabilitation and thereby minimize the impact of deprived sensory inputs on development.[13,16] The aim of this study was to assess the temporal bone CT scans of children with CHARGE syndrome, to describe in detail their otologic anomalies, and to determine if the CT findings correlate with the audiologic findings.

METHODS

We performed a retrospective review of medical records for the period 1990-2011 and identified 12 patients with CHARGE syndrome who underwent temporal bone CT and/or magnetic resonance imaging (MRI) for evaluation of their hearing loss at Princess Margaret Hospital for Children in Western Australia. To reduce interobserver bias, a single consultant radiologist who has a special interest in pediatric otorhinolaryngology completed a standardized questionnaire (Table 1) for each patient. The definitions of the various abnormalities are summarized in Table 1. The results were analyzed with the Statistical Package for Social Sciences program (IBM).

RESULTS

Twenty-four temporal bones were analyzed. However, CT imaging was not available for 4 temporal bones, and the bony details could not be described from the MRI. Some patients only had CT of the nasal cavity for investigation of the choanal atresia.

The cochlea abnormalities are summarized in Table 2. The internal auditory canal was normal in 83.3% (n=20) of ears. Three (12.5%) ears had enlarged basal turns and 4 (16.7%) each had hypoplastic and incompletely partitioned apical turns. The majority (n=13, 56.5%) of the vestibules were dysplastic. Only 1 bone of the 20 for which the bony details could be determined (5%) showed an enlarged vestibular aqueduct. Three bones (15%) had a reversed vestibular aqueduct angle.

The main abnormality of the lateral semicircular canal (LSCC) was the presence of only a bud in 10 (41.7%). Seven ears (29.2%) had a normal LSCC present, in 4 ears (16.7%) the LSCC was absent, 1 ear (4.2%) was dysplastic, and 2

Table 1. CHARGE Computed Tomography Questionnaire

Structure	Definition of Abnormality
Cochlea	
Internal auditory canal	Small/Normal
Aperture	Normal/Trapped
Basal turn	Normal/Dysplastic/Enlarged
Apical turn	Normal/Hypoplastic/Enlarged/Incomplete partition/Probable partition/Dysplastic
Vestibule	Normal/Hypoplastic/Dysplastic/Dilated/Common cavity
Vestibular aqueduct	Normal/Hypoplastic/Dysplastic/Dilated/Common cavity
Vestibular aqueduct angle	Normal/Large/Short/Reversed angle
Semicircular canal	
Lateral semicircular canal	Absent/Present/Bud
Posterior semicircular canal	Absent/Present/Bud
Superior semicircular canal	Absent/Present/Bud
Middle ear	
Cleft	Small/Normal
Middle ear cleft opacification	Yes/No
Ossicles (all 3)	Normal/Dysplastic/Absent
Ankylosis	Yes/No
Partial fusion of dysplastic malleus and incus	Present/Absent
Tegmen	Normal/Dehiscent
Round window	Normal/Aplasia/Small
Oval window	Normal/Aplasia/Small
Stapedius muscle	Normal/Aplasia/Small
Pyramidal eminence	Present/Absent
Tympanic sinus	Present/Absent
Seventh cranial nerve	
Labyrinth portion	Normal/Posterior
First genu	Normal/Posterior/Diagonal course
Tympanic portion	Normal/Prolapsed or inferiorly displaced
Mastoid portion	Normal/abnormal
External auditory canal	Wide/Narrow/Normal
Venous anomaly	Normal/Petrosquamous sinus
Jugular foramen	Normal/Diverticulum

Table 2. Cochlea Abnormalities

Type of Abnormality	Temporal Bones Affected, n (%)
Internal auditory canal	
Normal	20 (83.3)
Small	4 (16.7)
Aperture	
Normal	13 (54.2)
Trapped	7 (29.2)
Deficient modiolus	1 (4.2)
Open	1 (4.2)
Narrow	2 (8.3)
Basal turn	
Normal	21 (87.5)
Enlarged	3 (12.5)
Apical turn	
Normal	16 (66.7)
Hypoplastic	4 (16.7)
Incomplete partition	4 (16.7)
Vestibule	
Normal	6 (26.1)
Hypoplastic	4 (17.4)
Dysplastic	13 (56.5)

ears (8.3%) were hypoplastic. The main abnormality of the posterior semicircular canal (PSCC) was a bud present in 10 ears (41.7%). Ten ears had a PSCC present, and the PSCC was absent in 4 ears (16.7%). The superior semicircular canal was present in 11 (45.8%) ears, absent in 4 (16.7%), a bud only in 8 (33.3%), and hypoplastic in 1 (4.2%).

The middle ear abnormalities are summarized in Table 3. The middle ear cleft was normal in 55% (n=11) of ears; up to 80% of the ears (16 of 20 ears) had some abnormality of the ossicles, and up to 70% had an abnormality of the facial nerve (7th cranial nerve) segments, especially in the labyrinthine segment. Seven ears (35%) had an opacified middle ear cleft, with 2 (10%) being postoperative. Cholesteatoma was identified in 1 patient, and another patient had a grommet present. Thirteen ears (72.2%) of the 18 that could be assessed had ankylosis of the ossicles. Two ears could not be assessed on the CT scan and 4 had MRI, so the bony detail could not be assessed. Tegmen was normal in the majority of the ears (n=18, 90%) and dehiscent in 2 ears (10%).

The labyrinthine segment of CN7 was posterior in 14 ears (70%). The first genu was posterior in 11 ears (55%). The tympanic segment was inferiorly displaced in 5 ears (25%). The mastoid segment of CN7 was bifid in 1 ear (5%) but was otherwise normal in the others.

The external auditory canal was narrow in 7 (35%). Petrosquamous sinus was present in 35% (n=7). Jugular diverticulum was identified in 1 ear (5%).

Five patients had no documented otorhinolaryngology review at Princess Margaret Hospital. Of the remaining patients, 3 had conductive hearing loss (mean pure tone

Table 3. Middle Ear Abnormalities

Type of Abnormality	Temporal Bones Affected, n (%)
Cleft	
Normal	11 (55)
Small	1 (5)
Enlarged	6 (30)
Postoperative	2 (10)
Malleus	
Normal	8 (40)
Dysplastic	1 (5)
Absent	3 (15)
Dysplastic ankylosed	3 (15)
Resected	1 (5)
Partial resection	1 (5)
Fixation	3 (15)
Incus	
Normal	8 (40)
Dysplastic	3 (15)
Absent	3 (15)
Dysplastic ankylosed	3 (15)
Resected	2 (10)
Deficient short process	1 (5)
Stapes	
Normal	15 (75)
Absent	2 (10)
Dysplastic ankylosed	1 (5)
Not visualized	2 (10)
Round window	
Normal	15 (75)
Small	2 (10)
Dysplastic	1 (5)
Unknown	2 (10)
Oval window	
Normal	9 (45)
Aplasia	5 (25)
Small	4 (20)
Unknown	2 (10)
Stapedius muscle	
Present	11 (55)
Absent	8 (40)
Small	1 (5)
Pyramidal eminence	
Present	12 (60)
Absent	8 (40)
Tympanic sinus	
Present	12 (60)
Absent	8 (40)

audiometry [PTA]=37 dB; range, 25-45 dB), and 2 of these patients had their hearing restored to normal with the insertion of myringotomy tubes. Four patients had sensorineural hearing loss (mean PTA=61 dB; range, 30-90 dB). The majority of patients received conservative management for their hearing loss. Two of the patients were siblings and had documented CHD7 mutations.

We found that the CT findings correlated poorly with the audiologic findings. Unfortunately, one-third of the patients did not have audiologic assessments at our institution. Of the 8 patients who had audiograms available for review, only slightly more than one-third of the patients (n=3) had audiologic findings correlating with CT findings. For instance, one patient had mild conductive hearing loss, but he only had a dysplastic incus. The remaining patients did not have audiograms that correlated with CT findings. For example, one patient had mild conductive hearing loss despite multiple abnormalities in the middle and inner ear.

DISCUSSION

CHARGE syndrome is thought to be the result of embryogenesis arrest in the first trimester from a dysblastogenetic and dysneurulative process related by a common pathogenic mechanism, resulting in disturbed neural crest development.[5,7,10,11,20,23,25,26] Genetic localization has been limited by the phenotypic heterogeneity, as well as inconsistent chromosomal rearrangements.[26] Disruption of more than one gene is thought to be necessary to generate the CHARGE phenotype, as critical developmental pathways must be robust to minimize errors.[18] As reported by Edwards et al, several investigators have suggested that CHARGE syndrome may reflect a polytrophic developmental field defect involving the neural crest cells or the neural tube itself.[16]

As stated earlier, a range of heterozygous mutations in the CHD7 gene on chromosome 8q12 has been identified and is reported in 60%-70% of cases.[5,17,18,25,27] The CHD proteins belong to a superfamily of proteins with a unique combination of functional domains thought to be a general controller of developmental gene expression, with pivotal roles in the early embryonic development by affecting chromatin organization, mesodermal patterning, and gene expression.[5,18,25,26] This regulatory element potentially affects a large number of developmental pathways, explaining the pleiotropic nature of its phenotypic spectrum.[5,25] In addition, a balanced translocation interrupting the SEMA3E gene located in 7q21, as well as a de novo missense mutation S703L of SEMA3E has also been found in patients with CHARGE syndrome.[5] We could only find 2 cases in our study population for whom the CHD7 gene mutation was documented in the patient notes.

As is reported in the literature, we found variability in the presentation of hearing loss. While CT findings correlated poorly with the audiologic findings, CT is still an important initial assessment of the patients' hearing. Correlation between CT findings and audiologic findings was confounded by the fact that one-third (n=4) of our 12 patients did not have their audiologic evaluation at our institution. Of the 8 patients who had audiology assessments, only 3 had types of hearing loss that concurred with their CT abnormalities of the middle and/or inner ear. The majority (n=5) of patients had hearing loss that did not correlate with their CT abnormalities.

The management of children with CHARGE syndrome is complex, requiring early evaluation and close attention of the multidisciplinary team involving otorhinolaryngologists, audiologists, speech therapists, developmental pediatricians, and geneticists.[3,12,19] Early identification of hearing deficits does not necessarily translate into early aiding as other life-threatening medical conditions often take precedence, and consistent hearing aid use is often delayed because of early prolonged hospitalization for these issues.[3,12,19,24] In addition, visual deficits and neurologic and developmental issues make behavioral hearing tests difficult to conduct.[16,19] Hearing aids may present a problem because of the external ear anomalies.[3,12] These patients often have fluctuation of hearing levels secondary to otitis media with effusion, with an incidence rate approaching 100%, requiring frequent hearing aid adjustments.[3,11,12,16]

This study has some limitations. Because this study was a retrospective medical record review, the information was dependent on the completeness of documentation by the otorhinolaryngologist and the audiologist. We could not determine the outcomes of the patients who did not have their otorhinolaryngology follow-up at Princess Margaret Hospital or of those who did not have CT imaging or only had a limited CT for investigation of the choanal atresia.

As more abnormalities of the middle and inner ear are being found with better CT imaging, the overall management of hearing loss can improve. A better understanding of the mixed hearing loss patterns observed in CHARGE syndrome can direct the conservative or surgical approach to managing a child's hearing loss.

CONCLUSION

The management of CHARGE syndrome requires management in a multidisciplinary setting to optimize outcome. While CT and audiologic findings correlate poorly, they are still important in the comprehensive evaluation of the patient.

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